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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO
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STERNE KESSLER GOLDSTEIN & FOX
1100 NEW YORK AVENUE NW
SUITE 600
WASHINGTON DC 20005-3934

EXAMINER	ART UNIT	PAPER NUMBER
NGUYEN,	1632	6

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1-40 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 1-40 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892
☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). 5
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, ~~PTO-948~~ substituted PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

Claims 1-40 are pending to which the following grounds of rejection are applicable.

Sequence Rules 1.821

The specification is objected under Sequence Rules 1.821 because the specification does not conform to the requirements of 37 CFR 1.821 because the specification contains DNA sequences (p. 41, for example) for which there is no indicated SEQ ID NO:__ identifier for the DNA sequences. The requirement for compliance in 37 CFR 1.821(c) is directed to "*disclosures* of nucleotide and/or amino acid sequences." (Emphasis added.) All sequence information, whether claimed or not, that meets the length thresholds in 37 CFR 1.821(a) is subject to the rules. Sequence rules 37 CFR 1.821(d) requires the use of SEQ ID No: even if the sequence is embedded in the text of the description or in the claims. This requirement is also intended to permit references, in both the description and claims, to sequences set forth in the "Sequence Listing" by the use of assigned sequence identifiers without repeating the sequence in the text of the description or claims.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

Claims 19-39 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims, absent the qualifying language of "isolated" or cultured *in vitro* include in its scope a human containing the cells transformed with the virus. A

claim including within its scope a human being is not considered patentable subject matter as the limited but exclusive property right in a human being is barred by the United States Constitution. See 1077 OG 24.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected because an attempt to incorporate subject matter into this application by reference to a US co-pending application without an identified serial number is improper because only allowed U.S. applications and U.S. Patents can be incorporated by reference. The presently pending claims are drawn to tissue-specific-conditional vectors, cells which produce the vectors, and methods of using the vectors. Thus, the claims are generic and do not exclude the vectors described in the working examples. An artisan, attempting to make and use the claimed tissue-specific-conditional vectors, would first look to the specification for guidance as to the construction and production of such vectors. However, given that the manufacture of plasmids PAVS21.TK1 and SE280-E1, which are fundamental to the construction of the tissue-specific adenovirus vectors (which is one of the claimed species recited in the claims) is described in Example 5 (p. 39) only by the improper incorporation of references to other, pending, patent applications which are not identified by any serial number, one skilled in the art

requires an undue experimentation to obtain the plasmid DNA in order to practice the claimed invention.

Claims 1-40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention drawn to a tissue-specific replication-conditional vector and method of using the tissue-specific replication-conditional vector for distributing a polynucleotide in a tissue *in vivo*.

The application indicates at page 7 that replication of the claimed vector is conditioned upon the presence of trans-acting transcriptional regulatory factors that permit transcription from a transcriptional regulatory sequence (heterologous), and that the regulatory sequence is specifically activated or derepressed in the target tissue so that the replication of the vector only proceeds in that tissue. The application further indicates that in a preferred embodiments of the invention, the replication-conditional vector is a DNA tumor viral vector, *e.g.*, herpesevirus, papovavirus, papillomavirus, and hepatitis virus vector, and that in the most preferred embodiment, the vector is an adenovirus vector (p. 9). The application provides guidance as to the construction of the claimed vectors, but does not demonstrate with evidence that any of the disclosed vectors comprising a tissue specific regulatory sequence(s) is specifically activated for replication in a target tissue. The state of the art exemplified by Vile *et al.* (Molecular Medicine

Today, Vol. 4, 2:84-92, 1998) indicates that development of effective transcriptionally targeted vectors remains unpredictable. For example, Vile *et al.* (p. 90, column 1) teach that "the relevant locus control regions/enhancer/silencer/promoter sequences that control expression can be distributed over many kbp and within chromatin domains that are difficult to reproduce within the context of the vector systems, and that "the combinations of these elements in certain configurations of these elements in certain configurations might be successful in the context of one vector (such as plasmid DNA), but their specificity might be altered or lost in a different context (such as retrovirus or adenovirus). Russel (European Journal of Cancer, Vol. 30A, 8:1165-1171, August 1994) states that "cell-specific utilisation of the albumin (liver specific) and immunoglobulin (B-cell specific) promoters has been demonstrated within non-replicating adenovirus genomes but cell specificity was partially lost after replication of the viral DNA", and that the stoichiometry and kinetic of gene regulation by cellular transcription factors must be known for engineering the promoters of replicating vectors for tissue-specific, transformation-dependent expression (p. 1168, column 2). Thus, it is not apparent how one skilled in the art determines which of the tissue-specific replication-conditional vectors recited in claim 1 is tissue specific for replication without undue experimentation on the basis of applicant's disclosure, particularly given the doubts expressed in the art of record. With regard to claims directed to tissue-specific replication-conditional adenoviral vectors (which is a preferred species of the claimed invention), the adenoviral genes, E1b, E2, E1A, and E4 (all essential for replication of adenovirus vectors) encode proteins whose functions are dissimilar with each other. Each of

these genes or regions require a certain level of expression to support adenoviral replication. Note also the application indicates at page 6 that expression levels of adenoviral genes essential for replication, *e.g.*, E1 and E4, must be carefully regulated in order to averse toxicity effect of the adenoviral genes upon the cells or tissues transformed with adenovirus vectors. Since it is known in the art that tissue-specific cellular promoters activate constitutive expression of a transgene in a target tissue, it is not apparent how the expression levels of E4 gene, for example, are regulated from the claimed adenoviral vectors in order to avoid the toxicity to transformed cells (due to uncontrollable expression of E4 genes) prior to the replication and growth of the replication-conditional adenovirus vectors. There is no discussion in the specification of expression levels necessary to achieve appropriate expression for specific replication in a target tissue or cells *in vitro* and/or *in vivo*. Note that the application indicates at page 9 that the most preferred vector of the claimed invention is an adenovirus vector.

With regard to claims 3 and 11 drawn to the use of specific heterologous tissue specific promoters in the construction of the claimed vectors, an artisan, attempting to make and use the claimed vectors, would first look to the specification for guidance as to the availability of heterologous tissue-specific transcriptional regulatory sequences recited claims 3 and 11. However, the specification is not enabling for the claimed vectors containing the promoters selected from group consisting of tyrosinase, CEA, surfactant, and ErbB2 (recited in claims 3 and 11). The specification indicates that the promoters can be cloned and sequenced by PCR technology using the primers depicted in Table 1, however, it is not apparent how one skilled in

the art clones, sequences, and employs the DNA sequence(s) encoding the functionally active promoters in the conditional replication vectors with a reasonable expectation of success and without undue experimentation, particularly since it is not apparent as to what is the length and the exact location of the DNA sequence(s) encoding the promoters, and as to whether there are more than one locus control regions and/or enhancers and/or silencers and/or promoter sequences involved in the make-up of the DNA sequences encoding the functionally active promoters recited in the claims. Note that Vile *et al.* (p. 90, column 1) teach that "the relevant locus control regions/enhancer/silencer/promoter sequences that control expression can be distributed over many kbp and within chromatin domains that are difficult to reproduce within the context of the vector systems".

Thus, one skilled in the art cannot identify, without undue experimentation, a tissue in which all of the replication-conditional vectors recited in claim 1 are specifically replicated *in vitro* and/or *in vivo* by means of the transcriptional regulatory sequence contained in the vectors, particularly given the reasons set forth in the preceding paragraphs.

As to claims 9-18 drawn to methods of distributing a polynucleotide in a tissue *in vivo* using the claimed vectors, the application on page 12 indicates that "the object of the distribution is to deliver the vector, gene product or the effects of the gene product (as by a bystander effect, for example) to substantially number of cells of the target tissue, so as to treat substantially the entire target tissue". Thus, the claims encompass gene-targeted therapy in any subject including a human and implanted cells containing the claimed vector for generating a therapeutic effect.

Major considerations for any gene transfer or gene therapy protocol involve issues such as amount of DNA constructs to be administered, what amount is considered to be therapeutically effective for all of the claimed nucleic acid molecules, the route and time course of administration, the sites of administration, successful uptake of the claimed DNAs at the target site, expression of the DNAs at the target site in amounts of effecting the claimed methods (Crystal, Science, Vol. 270:404-409, 1995; Coghlan, New Scientists, Vol. 148:14-15, 1995). Gunzburg *et al.* (Molecular Medicine Today, pp. 410-417, 1995) state that "clearly, there are many problems to be overcome before gene therapy becomes a widely used treatment , and it will probably only ever complement rather than replace existing therapies" (p. 417). Gunzburg *et al.* also state that "the efficiency of gene delivery is perhaps the most limiting technical problem; this will require extensive modifications to existing vector systems or even the construction and development of new gene delivery systems (p. 416, column 2, last paragraph). Regarding the state of the art of gene therapy for human cancer, Mastrangelo *et al.* (Seminars in Oncology, Vol. 23, No. 1:4-21, 1996) states that "to date the major successes with gene therapy for cancer have been limited to *in vitro* systems where tumor cells with well defined genetic defects are easily targeted" (p. 13, column 2). Mastrangelo *et al.* further state that "Critical to the success of gene therapy is the efficient transfer (transfixing) of a functioning gene to the target cell" and that "this has prevented a major stumbling block, particularly for *in vivo* gene transfer" (p. 10, column 1). Regarding *ex vivo* gene therapy, Mastrangelo *et al.* disclose that adoptive immunotherapy (*e.g.* infusion of cytotoxic cells such as genetically modified macrophage cells),

which has been known to be effective *in vitro*, is not necessarily effective *in vivo* (pp. 18-19). Ledley (Human Gene Therapy 6:1129-1144, 1995) states that "every somatic target exhibits distinct properties, and the rate-limiting steps in gene delivery and expression may be expected to be different" and that "it is unlikely that any one method for gene transfer will prove to be effective in every organ" (p. 1139). While the specification provides a list of such promoters, there is no guidance as to those specific promoters which could be taken and used in the claimed vectors. It is a necessary element of the claimed invention that the tissue specific promoters express the gene necessary for replication sufficient to foster replication specifically in a disease site, with the result of *in vivo* gene expression so as to have a therapeutic effect. Thus, a showing of promoters and promoter regions that provide such specificity and such sufficiency is necessary for the implementation of the invention. A listing of promoters known in the art at the time of filing may provide a germ of an idea, but that is not sufficient guidance to apply the promoter to vector and obtain specific vector replications and sufficient transgene expression at a target tissue *in vivo* so as to generate a therapeutic effect. Thus, without guidance from the specification the artisan would have been required practice undue experimentation to construct and use the claimed vectors.

In view of the lack of guidance regarding the administration parameters, lack of convincing data or working examples, breadth of the claims, state of the art and the unpredictability of the art, as set forth by the evidence presented above, undue experimentation would be required by one of ordinary skill to practice the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112, second paragraph:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the application regards as his invention.

Claims 1-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-8, and 19-40 are indefinite in the recitation of the term "capable of" since it not clear as to what exactly encompassed by the term, and since "capable" is only "capacity" and does not indicate per se that tissue-specific replication occurred.

Claims 10 and 11 are vague and indefinite since the claims refer to the vector of claim 9; however, claim 9 is directed to a method claim. For the purpose of compact prosecution, it is assumed that claims 9 and 10 refer to the method of claim 9.

Claims 19-28, and 30-39 are indefinite in the recitation of "a cell" since it is not apparent whether the cell is directed to an isolated cell or whether the cell is an implanted cell *in vivo.*

Claims 9-17 are indefinite because it is not apparent as to what is the stated effect of the distribution of a polynucleotide *in vivo* in accomplishing a beneficial effect. Furthermore, claim 17 is indefinite because it is not apparent as to what is the stated effect of *in vivo* gene expression of a heterologous gene in accomplishing a beneficial effect.

Claim 18 is indefinite because it is not apparent as to what are the metes and bounds of the anti-tumor activity of "said heterologous gene product". Does the anti-tumor activity cure, prevent, stimulate, or inhbit the growth of a tumor in all target tissues *in vivo*?

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5, 8-14, 17-24, 27-35, and 38-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martuza *et al.* (US Pat No. 5,728,379).

Martuza *et al.* disclose a method for killing tumor cells *in vivo* comprising administration of tissue-specific-replication competent herpes simplex virus vectors to tumor cells. The tissue-specific-replication competent herpes simplex virus vectors contain a tissue-specific or cell-

specific transcriptional regulatory sequence that is operatively linked to an essential herpes simplex virus gene, wherein said transcription regulatory sequence effects expression of said gene in a specific tissue or cell, such that said virus replicates only in said tissue or cell. Claims 1-13 are directed to the method and the replication competent herpes simplex virus vectors. The claimed invention of the '379 patent is fully disclosed and enabled by the specification of the parent U.S. Pat No. 5,585,096. In the '096 patent, columns 11 and 12 disclosed the tissue-specific-replication competent herpes simplex virus vectors and methods of using the herpes simplex virus vectors to express a heterologous gene for specific killing of tumor cells. Columns 15 and 16 provide a guidance as to how to construct and produce the tissue-specific-replication competent herpes simplex virus vectors. Examples 2-5 provide a detailed description as to how to use the replication-competent viral vectors in *in vivo* extracranial and *in vivo* intracranial tumor killing models. Given that tissue-specific promoters selected from group consisting of α-fetoprotein, DF3, tyrosinase, and ErbB2 are known in the art prior to the effective filing date of the as-file application (see Tables 1 and 2 of the '379 patent), it would have been obvious for one of ordinary skill in the art to have constructed and employed the tissue-specific-replication competent herpes simplex virus vectors of Martuza *et al.* using a known tissue-specific promoter operably linked to a viral gene necessary for herpes simplex virus replication for expressing a heterologous gene, *e.g.*, cytokines, in a tumor cell-specific fashion in order to target an immune response that kills the tumor cells. One of ordinary skill in the art would have a reasonable expectation of success in constructing and employing the tissue-specific-replication competent

herpes simplex virus vectors of Martuza *et al.* for distributing and expressing a polynucleotide at a tissue *in vivo,* particularly given that claims 1-13 of the '379 patent recite the same.

Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

Claims 1-5, 8-14, 17-24, 27-35, and 38-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martuza *et al.* (US Pat No. 5,585,096).

Martuza *et al.* disclose and a method for killing tumor cells *in vivo* comprising administration of tissue-specific-replication competent herpes simplex virus vectors to tumor cells. The tissue-specific-replication competent herpes simplex virus vectors contain a tissue-specific or cell-specific transcriptional regulatory sequence that is operatively linked to an essential herpes simplex virus gene, wherein said transcription regulatory sequence effects expression of said gene in a specific tissue or cell, such that said virus replicates only in said tissue or cell. Columns 11 and 12 disclosed the tissue-specific-replication competent herpes simplex virus vectors and methods of using the herpes simplex virus vectors to express a heterologous gene for specific killing of tumor cells. Columns 15 and 16 provide a guidance as to how to construct and produce the tissue-specific-replication competent herpes simplex virus vectors. Examples 2-5 provide a detailed description as to how to use the replication-competent viral vectors in *in vivo* extracranial and *in vivo* intracranial tumor killing models. Given that tissue-specific promoters selected from group consisting of α-fetoprotein, DF3, tyrosinase, and ErbB2 are known in the art prior to the

effective filing date of the as-file application (see Tables 1 and 2 of the '379 patent), it would have been obvious for one of ordinary skill in the art to have constructed and employed the tissue-specific-replication competent herpes simplex virus vectors of Martuza *et al.* using a known tissue-specific promoter operably linked to a viral gene necessary for herpes simplex virus replication for expressing a heterologous gene, *e.g.*, cytokines, in a tumor cell-specific fashion in order to target an immune response that kills the tumor cells. One of ordinary skill in the art would have a reasonable expectation of success in constructing and employing the tissue-specific-replication competent herpes simplex virus vectors of Martuza *et al.* for distributing and expressing a polynucleotide at a tissue *in vivo,* particularly given that columns 15, 16, and Examples 2-5 provide a detailed description as to how to construct and employ such vectors for killing tumor cells in a specific fashion.

Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

Claims 1-8, and 19-42 are rejected under 35 U.S.C. 102(b) as being anticipated by, or in the alternative, under 35 U.S.C. 103 as being unpatentable over Babiss *et al.* (J. Mol. Biol. 193, 643-650, 1987).

Babiss *et al.* teach a replication competent adenovirus where the promoter for albumin gene, a liver specific promoter, regulates the expression of E1a and E1b in liver cells (p. 645, col. 2, lines 1-19). Babiss *et al.* indicate that the vector can be used in assays to determine the effect

of replication on the expression of endogenous genes (p. 649, col. 1, lines 4-8). Fig. 2 depicts transcription pattern in HepG2 cells after infection by alb194 virus. Column 2 at page 645 states that "injection with the abl454 virus, which includes the E1A enhancer upstream from the albumin promoter and results in a five fold increase in transcription rate from the exogenous albumin promoter on the virus". To the extent that the reference is ambiguous regarding the use of a tissue specific promoter selected from group consisting of α-fetoprotein, CEA, DF3, tyrosinase, and ErbB2, it would have been obvious for one of ordinary skill in the art at the time of the invention to make the adenoviral vector of Babiss *et al.* by employing any of the known tissue-specific promoters such as α-fetoprotein, CEA, DF3, tyrosinase, and ErbB2, particularly since Tables 1 and 2 of the '379 patent indicate that such promoters are known and available at the time the invention was made. Thus, absent evidence to the contrary, and in the alternative, the adenoviral vector of Babiss *et al.* has all of the properties cited in the claims.

Double Patenting

1. The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel,* 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornum,* 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi,* 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman,* 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. **Claims 1-40** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable claims 1-42 of US application No. 08/487,992. Although the conflicting claims are not identical, they are not patentably distinct from each other because both set of claims are directed to drawn to a tissue-specific replication-conditional vector, isolated cells containing the tissue-specific replication-conditional vector, method of producing the vectors, and methods of using the tissue-specific replication-conditional vector for distributing a polynucleotide in a tissue *in vivo.*

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Jacqueline Stone*, may be reached at **(703) 305-3153**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 304-0196**.

Dave Nguyen

April 7, 1998

CHRISTOPHER S. F. LOW
PRIMARY EXAMINER
GROUP 1800 1600